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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,414	08/30/2005	Johannes M. Van Den Brink	4560-4	7936

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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,414	VAN DEN BRINK ET AL.	
	Examiner	Art Unit	
	Michele K. Joike, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-19,22 and 23* is/are rejected.

7)☒ Claim(s) *6,7,20 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/17/04, 8/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The IDS submitted on August 30, 2005 has been considered. The IDS submitted on December 17, 2004 has been considered, except for the last NPL reference. The last reference has not been considered because the author's name is incorrect and there is no source listed for the article.

Specification

The abstract of the disclosure is objected to because the word "said" is used in the Abstract in line 2.

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The

disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc..

Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: the sequence identifiers in the specification should correspond to the sequence identifiers in the sequence listing. For example, SEQ ID XXX-1 should be SEQ ID NO: 3, as stated in the sequence listing.

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

MPEP § 2442(d).

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by US 6,127,142.

Applicants claim an active bovine chymosin comprising a N-X-T glycosylation site.

US 6,127,142 (specifically columns 1-3, and 6) teaches an aspartic protease used for clotting milk (column 1, lines 34-40). The protease should have an activity ratio similar to bovine chymosin (column 6, lines 38-41), the implication being that bovine chymosin is acceptable to use as the protease. The modified aspartic protease has a glycosylation site, which can be the sequence N-X-T (column 3, lines 38-41).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 8, 12-19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,800,849, in view of Kasturi et al and in further view of US 6,127,142.

Applicants claim a process for producing an isolated polynucleotide sequence encoding a modified aspartic protease comprising modifying the polynucleotide sequence to encode an extra N-X-T glycosylation site in the aspartic acid protease amino acid sequence, and isolating the polynucleotide sequence. The aspartic protease is a bovine prochymosin. The modified aspartic protease can also have an artificial linker comprising the N-X-T glycosylation site. Applicants also claim the isolated polynucleotide sequence encoding the modified aspartic protease. Further, the Applicants claim a method of producing the modified aspartic protease by cultivating an *Aspergillus* cell comprising the polynucleotide sequence so that the modified aspartic protease is produced and active. Lastly, Applicants claim an active bovine chymosin comprising a N-X-T glycosylation site.

US 5,800,849 (specifically columns 1-3, Ex. 1) teaches a process for producing cheese by adding an aspartic protease to clot milk (Abstract). The process includes isolating a DNA sequence encoding a bovine prochymosin and transforming it into *Aspergillus* (column 1, lines 37-40, 54, and 55-56). The prochymosin has an N-bound glycosylation site (column 3, lines 11-15). After the DNA sequence encoding the aspartic protease was transformed into a cell, and the protease was produced, the protease was recovered and used to make cheese, so was therefore active (Ex. 1).

US 5,800,849 does not teach the glycosylation site being N-X-T.

Kasturi et al (Biochem. J. 323: 415-419, 1997, specifically pp. 415-416) teach an N-linked glycosylation protein. The glycosylation site is N-X-T, and can be mutated by site-directed mutagenesis, and therefore be an artificial linker. However, Kasturi et al do not teach a N-linked aspartic protease.

US 6,127,142 (specifically columns 1-3, and 6) teaches an aspartic protease used for clotting milk (column 1, lines 34-40). The protease should have an activity ratio similar to bovine chymosin (column 6, lines 38-41), the implication being that bovine chymosin is acceptable to use as the protease. The modified aspartic protease has a glycosylation site, which can be the sequence N-X-T (column 3, lines 38-41).

The ordinary skilled artisan, desiring to use a N-X-T glycosylation site in chymosin would have been motivated to combine the teachings of US 5,800,849 of process of isolating a DNA sequence encoding a N-glycosylated bovine prochymosin and transforming it into *Aspergillus* with the teachings of Kasturi et al of an N-X-T linked protein and of US 6,127,142, of a modified aspartic protease that has a glycosylation site of N-X-T, because Kasturi et al teach that N-linked glycosylation usually occurs at N-X-S/T sites, and N-glycosylation profoundly affects a protein's expression and function. It would have been obvious to one of ordinary skill in the art to use a N-X-T site because N-X-T sites are generally better oligosaccharide acceptors than N-X-S sites (Kasturi et al, p. 418). Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 9-11 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,800,849, Kasturi et al and US 6,127,142 as applied to claims 1-5, 8, 12-19 and 22 above, and further in view of Korman et al.

Applicants claim a process for producing an isolated polynucleotide sequence encoding a modified aspartic protease comprising modifying the polynucleotide sequence to encode an extra N-X-T glycosylation site in the aspartic acid protease amino acid sequence, and isolating the polynucleotide sequence. The aspartic protease is a bovine prochymosin. Additionally, the aspartic protease can comprise alpha-amylase as a fusion partner, wherein the artificial linker is situated between a pro-sequence and the fusion partner. Applicants also claim the isolated polynucleotide sequence encoding the modified aspartic protease. Further, the Applicants claim a method of producing the modified aspartic protease by cultivating an *Aspergillus awamori* cell comprising the polynucleotide sequence so that the modified aspartic protease is produced and active. Lastly, Applicants claim an active bovine chymosin comprising a N-X-T glycosylation site.

US 5,800849, Kasturi et al and US 6,127,142 teach all of the limitations as described above. However, they do not teach that the aspartic protease can comprise alpha-amylase as a fusion partner, wherein the artificial linker is situated between a pro-sequence and the fusion partner. They also do not teach transformation of an isolated polynucleotide sequence encoding a modified aspartic protease in to *Aspergillus awamori.*

Korman et al (Curr. Genet. 17: 203-212, 1990, specifically pp. 203, 204, 212 and figure 5) teach a vector with a gene fusion of alpha-amylase and bovine prochymosin transformed into *Aspergillus awamori* (Materials & Methods). A synthetic DNA linker encoding the last five codons of the *amyA* gene and the first six codons of prochymosin were used to join the *amyA* and prochymosin genes (figure 5). Co-transformants were screened for chymosin production.

The ordinary skilled artisan, desiring to have an aspartic protease comprising an alpha-amylase as a fusion partner, wherein an artificial linker is situated between a pro-sequence and the fusion partner would have been motivated to combine the teachings of US 5,800,849 of process of isolating a DNA sequence encoding a N-glycosylated bovine prochymosin and transforming it into *Aspergillus*, and the teachings of Kasturi et al of an N-X-T linked protein and of US 6,127,142, of a modified aspartic protease has a glycosylation site of N-X-T, with the teachings of Korman et al teaching a gene fusion of alpha-amylase and bovine prochymosin with a synthetic DNA linker encoding the last five codons of the *amyA* gene and the first six codons of prochymosin because Korman et al teach that the alpha-amylase gene promoter has been used to derive high level expression of an aspartic protease gene from fungi (p. 203). It would have been obvious to one of ordinary skill in the art to use alpha-amylase as a fusion partner because gene fusions are useful in studying the regulation of genes, and the potential use of *amyA* transcriptional and translational control elements in combination with aspartic proteases has been demonstrated (p. 212). Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it

must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

Claims 6, 7, 20 and 21 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike, Ph.D. whose telephone number is 571-272-5915. The examiner can normally be reached on M-F, 9:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nancy T. Vogel/
Primary Examiner, Art Unit 1636

Michele K Joike, Ph.D.
Examiner
Art Unit 1636